REMARKS

Claim 76 is pending in the instant application and is currently subject to (1) an obviousness rejection under 35 U.S.C § 103(a) in light of US Patent 5,538,733 to Emery et al. ("Emery") and US Patent 4,687,001 to Arko ("Arko"), and (2) a rejection under 35 U.S.C. § 112, second paragraph for being indefinite . Applicants have amended claim 76 to indicate that the passive diffusion of "the antigen or an immune cell secretory product or co-stimulatory factor" is prevented by the container. This amendment is supported by the specification at page 14, lines 1-22. Applicants respectfully request that the above amendment and following remarks be made part of the record in the file history of the instant application.

I. Rejection for Obviousness Under 35 U.S.C. § 103(a) Should be Withdrawn

Claim 76 is rejected under 35 U.S.C. § 103(a) as being obvious over Emery in view of Arko. In particular, the Examiner asserts that Emery discloses antigens in a time-delay matrix. The Examiner further argues that the present invention is obvious over Emery in view of Arko, because Arko teaches a chamber for use as an infection site and it would have been obvious to one of ordinary skill in the art to combine the teachings of Emery and Arko to develop the current device for use in the claimed method. The Applicants respectfully disagree, for the reasons discussed below.

A. The Legal Standard

A finding of obviousness requires that "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. §103(a). To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the prior art references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. M.P.E.P. 2143.

In its recent decision addressing the issue of obviousness, *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 USPQ2d 1385 (2007), the Supreme Court affirmed that it is "important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does . . . because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." *KSR*, 127 S.Ct. at 1741, 82 USPQ2d at 1396. Thus, consistent with the principles enunciated in *KSR*, a *prima facie* case of obviousness can be established by showing a suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference *and* to carry out the modification with a reasonable expectation of success, viewed in light of the prior art.

Both the suggestion and the reasonable expectation of success must be found in the prior art and *not* be based on the applicant's disclosure. *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988). With regard to the final point, the *KSR* Court citing *Graham*, upheld the principle of *avoiding hindsight bias* and cautioned courts to *guard against reading into the prior art the teachings of the invention in issue.* 127 S.Ct. at 1742, 82 USPQ at 1397.

B. The Invention

The present invention relates to a method of immunizing a mammal for the preparation of hybridomas for the production of monoclonal antibodies against an antigen. The method involves implanting within a mammal a novel device that has a porous matrix that contains an antigenwith a container having means for limiting passive diffusion of an antigen and immune cell secretory products and co-stimulatory factors out of the device. The diffusion barrier that maintains optimal levels of antigen, immune cell secretory products and immune cells within the device. Page 14, lines 2-7.

C. <u>The Claimed Invention Is Non-Obvious</u>

Claim76 is rejected under 35 U.S.C. 103(a) as being obvious in light of Emery and Arko.

According to the Office Action, Emery et al. teaches the implantation of antigens in a time delayed matrix to elicit an immune reaction in an animal.

However, Emery et al. does not disclose an implant having a perforated impermeable container/diffusion barrier of the present invention. Emery et al. discloses a solid implant comprised of biocompatible, biodegradable, bioabsorbable and/or bioerodible polymeric material that will release an immunogenic agent for sustained delivery into the surrounding tissue fluids. (Col. 2, Line 15-37). Further, Emery et al. teaches the release of antigens into the surrounding tissues as opposed to retaining a concentration of antigens within the device, and therefore the use of a diffusion barrier would be contrary to the aims of the Emery implant. However, in the implant of the present invention, "the antigen is retained within the device and its concentration remains high, as do the concentrations of co-stimulatory factors secreted by the cell population with[in] the device, much in the same fashion as within a lymph node." (Page 14, Lines 20-22) The present invention utilizes the perforated impermeable container/diffusion barrier to limit the passive diffusion of the antigens out of the device and thereby maintain a high concentration of antigens and small molecules within the device. Thus, Emery et al. does not disclose the implantation of a device containing a porous matrix for an antigen within a perforated impermeable container/diffusion barrier as part of a method of immunizing a mammal for the purpose of ultimately producing monoclonal antibodies.

Accordingly, the Examiner relies on Arko for the teaching of a container/chamber for use as an infection site from which fluids can be collected, and claims that the combination of Emery and Arko would render the device of the current method claim obvious.

Arko discloses the use of an improved subcutaneous implant apparatus that reduces discomfort to the animal and is conveniently accessible for studying the infectous disease process of microorganisms in the animal. (Col. 2, Lines 3-8). The subcutaneous implant consists of a cylindrical chamber of pliable material that is adapted to expand or collapse as fluids are injected into or removed from the chamber. (Col. 4, Lines 5-8). Thus, unlike the device of the current application the chamber does not contain a porous matrix with the antigen. Arko notes that a further object is to provide an implant that is intended to be inserted in a flattened configuration into the animal and expand thereafter to provide the necessary chamber for evaluating immune

reactions. (Col. 3, Lines 50-61). Furthermore, Arko surmises that the subcutaneous implant apparatus permits the experimental disease element to establish itself by preventing the retaining within the chamber certain serum components. (Col. 4, Lines 33-37).

The Applicants disagree with the Examiner's contention that one of ordinary skill in the art would combine the teachings of Emery and Arko to arrive at the implantable device used in the current method claims. The Emery device lacks an essential element of the device used within the claimed method, *i.e.*, a container with means for limiting passive diffusion. Whereas, the Arko device lacks the porous matrix for containing an antigen of the device used in the claimed method.

The Examiner alleges that one of ordinary skill in the art would not be motivated to combine the teachings of Emery and Arko to arrive at the device of the current invention. However neither Emery nor Arko provide any motivation for such a combination and further the alleged combination would frustrate the goals of the respective devices. First, Emery seeks to release the antigen into the circulation of an animal to prime the immune response in an animal (Col. 3, Lines 60-65), whereas Arko alleges that its subcutaneous implant allows the infectious agent to establish itself within the container by inhibiting the release of certain serum factors into the surrounding tissues. (Col. 4, Lines 33-37). Given that Emery teaches the release of the antigen to circulate within the animal there would be no motivation to provide a container/chamber that would interfere with the passive diffusion of the antigen out of the device. Further, the incorporation of the container of Arko over the solid implant of the Emery device would be contrary to the goals of Emery. Second, Arko teaches a pliable container that can be flattened in order to provide for easy insertion into an animal and that can expand or collapse as fluids are injected into or removed from the implant chamber. Thus, one of ordinary skill in the art would have no motivation to incorporate a solid implant into the chamber used in the Arko device since the solid implant would interfere with the pliability of the Arko device. A less pliable device would contravene the goals of Arko – to ease discomfort to the animal and prevent ejection of the device due to subcutaneous pressure necrosis. Thus, the claimed invention is not obvious in light of Emery and Arko.

The references cited by the Examiner do not suggest or provide motivation for the presently claimed invention, let alone to do so with an expectation of success. The devices of Emery and Arko are different than the device used within the present method of immunizing a mammal for the

preparation of a hybridoma for the production of a monoclonal antibody. The Emery device consists of a solid implant without a container that acts as a means of limiting passive diffusion, and the Arko device lacks a porous matrix for containing an antigen. The incorporation of elements of the Arko device in the Emery device and vice versa would be contrary to the teaching of these patents and would frustrate the stated goals of Arko and Emery. In contrast, the novel method of the present invention immunizes an animal by implanting a device that enables contact between immune cells and antigen within the porous matrix of the device without permitting the antigens and co-stimulatory factors from diffusing out. Given the difference in the devices of Emery and Arko and the device used in the method of the present invention, the combination of a matrix with a container that limits passive diffusion, would not have been obvious to one of ordinary skill in the art at the time the invention was made.

In view of the remarks above, the Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 103(a). In the alternative, the Applicants respectfully request that the Examiner support the conclusion of obviousness based on knowledge within the level of ordinary skill in the art by an affidavit pursuant to rule 37 CFR 1.104(d)(2).

II. Rejection for Indefiniteness Under 35 U.S.C. § 112, Second Paragraph Should Be Withdrawn

The Examiner has rejected Claim 76 under 35 U.S.C. § 112, second paragraph, as being indefinite. In particular, the Examiner alleges that there is no antecedent basis for "molecule" and that the term "molecule" is indefinite. Without agreeing with the indefiniteness rejection, Applicants have amended claim 76 to replace "molecules" with "the antigen or an immune cell secretory product" for the sake of advancing the prosecution. These amendments are supported by the specification at page 14, lines 1-22. Applicants respectfully request the withdrawal of the rejection under 35 U.S.C. 112, second paragraph.

CONCLUSIONS

Applicants respectfully request that the foregoing remarks be made of record in the file history of the instant application. Applicants submit that the remarks and amendments made herein now place the pending claims in condition for allowance. If a telephone discussion will help expedite processing of this application, the Examiner is invited to telephone the undersigned at (914) 762-7586.

Respectfully submitted,

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